DOSING OF DRUGS: DOSAGE REGIMENS AND DOSE-RESPONSE

Chyung S. Cook
Aziz S. Karim
Pharmacia Corporation, Skokie, Illinois, U.S.A.

INTRODUCTION

Drugs are administered for their pharmacological effects. In some cases, however, drug therapy includes the risk of undesirable side effects, with each drug having inherently different risks associated with its use. Therefore, it is the objective of physicians to administer a drug with an optimal dosing regimen by selecting the appropriate dosage, route, and frequency of administration to achieve maximal pharmacological efficacy with minimal side effects.

In most clinical situations, drugs are administered either repetitively, at time intervals, or as a continuous infusion to maintain a certain blood concentration at steady state within the known therapeutic concentration range for a given drug. A loading dose may be desirable in order to achieve the target concentration rapidly at the onset of therapy for a drug with a long half-life. These maintenance and loading doses as well as dosing frequency can be determined using pharmacokinetic principles.

DETERMINATION OF DOSE

Maintenance Dose

The general principle that is used to select the appropriate maintenance dose and dosing interval for the average patient is as follows: to maintain a target concentration at the steady state, the rate of drug administration should be equal to the rate of elimination. This can be expressed by the following equation (Eq. 1) using the clearance concept:

$$\text{Dosing rate} = (\text{CL}F) \times C_{ss} \quad (1)$$

where CL is clearance, C_{ss} is the steady state concentration of drug, and F is the fraction of the dose that is systemically available. Therefore, if CL, F, and C_{ss} are known, then the appropriate dose and dosing interval can be calculated.

For example, for theophylline, the clearance value is 0.65 mL/min/kg (2.34 L/h for a 60 kg man), the half-life in healthy nonsmoking asthmatics is approximately 9 h and the effective plasma concentration range is 5–15 mg/L. Because the dose is an IV infusion, the systemic availability, F is 1. If the target plasma concentration at the steady state is 10 mg/L, then the

$$\text{IV infusion rate for a 60 Kg man} = 2.34\,L/h \times 10\,mgL = 23.4\,mgh.$$

If the dose is administered not as an infusion but as a bolus dose (e.g., IV injection or an oral dose), high fluctuations in plasma concentrations between peak (C_{max}) and trough values (C_{min}) will occur. If absorption and distribution are very rapid, fluctuation of plasma concentrations between C_{max} and C_{min} values will be controlled almost entirely by the elimination of the half-life. When the dosing interval is the same as the half-life, the ratio of C_{max}/C_{min} is 2, which is usually tolerable as long as pharmacological activity is directly correlated with plasma concentrations.

Using theophylline as an example again, if the targeted average plasma concentration is 10 mg/L, the dose calculated in the above example is 23.4 mg/h. Therefore, to maintain this concentration as an average concentration, IV bolus doses can be given at 140 mg every 6 h (qid), 187 mg every 8 h (tid), 280 mg every 12 h (bid), or 560 mg once a day (qd). The average concentration for a noninfusion dose regimen is defined as

$$\text{Average plasma concentration} = \text{AUC}/\tau \quad (2)$$

where AUC is the area under the plasma concentration–time curve and τ is dosing interval.

Although all these dose regimens will give the same target average plasma concentration, both $C_{ss,max}$ and $C_{ss,min}$ values will be markedly different. For a given dose, $C_{ss,max}$ and $C_{ss,min}$ values can be estimated using the following equations (Eqs. 3 and 4). Alternatively, the dose that will give the targeted maximal and minimal concentrations can be estimated using these equations:

$$C_{ss,max} = \frac{F \cdot \text{Dose} \cdot e^{-KT_{max}}}{V_{ss}(1 - e^{-K\tau})} \quad (3)$$

$$C_{ss,max} = \frac{K_a \cdot F \cdot \text{Dose} \cdot e^{-K\tau}}{V_{ss}(K_a - K)(1 - e^{-K\tau})} \quad (4)$$

K is the elimination rate constant (equal to 0.693 divided by the clinically relevant half-life). K_a is the absorption rate constant. T_{max} is the time to reach C_{max}. V_{ss} is the volume of distribution at steady state.

For an IV dose, T_{max} is 0, and the term $e^{-KT_{max}}$ becomes 1 in Eq. 3. The term $K_a/K_a - K$ in Eq. 4 also becomes 1. The term $e^{-K\tau}$ is the fraction of the last dose that remains in the body at the end of a dosing interval.

For theophylline (V_{ss} for 60 kg man = 30 L, $K = 0.077\,h^{-1}$, and τ = 6, 8, 12, or 24 h), the calculated C_{max}, C_{min} and C_{max}/C_{min} values for IV doses are as follows:

Dose regimen	C_{max} (mg/L)	C_{min} (mg/L)	C_{max}/C_{min}
140 mg qid	12.6	8.0	1.6
187 mg tid	13.6	7.3	1.9
280 mg bid	15.5	6.1	2.5
560 mg qd	22.2	3.5	6.3

Because theophylline has a relatively narrow therapeutic index, it would be desirable to determine a dose at which the maximal and minimal concentrations at steady state will be within the therapeutic concentration range (5–15 mg/L). Therefore, the 280 mg bid dose regimen is convenient and adequate to achieve C_{max} and C_{min} within the therapeutic range.

As can be seen in the table, the more frequently a drug is given, the smaller the ratio of peak-to-trough plasma concentrations will be. These phenomena are also demonstrated by the computer-simulated plasma concentration-time curves (Fig. 1). If the dosing interval is equal to or smaller than the half-life, then the fluctuation between C_{max} and C_{min} is usually acceptable even for a drug with a narrow therapeutic window. If the dosing interval is greater than the half-life, a large fluctuation is expected, which may not be desirable for drugs with a narrow therapeutic window. However, if the half-life is very short, dosing at every half-life is not practical. Therefore, different formulations (e.g., extended-release or controlled release) are often used. For drugs with a long half-life (greater than 12 h), the dose can be given once or twice a day to maintain appropriate therapeutic levels.

Following multiple oral doses of a drug that obeys bi-exponential kinetics after IV administration (two-compartment model), the estimation of the $C_{ss,max}$ and $C_{ss,min}$ involves a complicated set of exponential constants for absorption and distribution, as shown below.

$$C_{ss,max} = \frac{F \cdot \text{Dose}(K_{21} - \alpha)e^{-\alpha T_{max}}}{V_{ss}(\beta - \alpha)(1 - e^{\alpha\tau})} + \frac{F \cdot \text{Dose}(K_{21} - \beta)e^{-\beta T_{max}}}{V_{ss}(\alpha - \beta)(1 - e^{\beta\tau})} \quad (5)$$

$$C_{ss,min} = \frac{K_a \cdot F \cdot \text{Dose}(K_{21} - \alpha)e^{-\alpha\tau}}{V_{ss}(K_a - \alpha)(\beta - \alpha)(1 - e^{\alpha\tau})} + \frac{K_a \cdot F \cdot \text{Dose}(K_{21} - \beta)e^{-\beta\tau}}{V_{ss}(K_a - \beta)(\alpha - \beta)(1 - e^{\beta\tau})}, \quad (6)$$

where α and β are rate constants for distribution and elimination phases, respectively, and K_{21} is the rate constant from tissue to plasma compartment.

As with the one compartment model, T_{max} is 0 for an IV bolus dose or rapid oral absorption, and both terms $e^{-\alpha T_{max}}$ and $e^{-\beta T_{max}}$ become 1 in Eq. 5. Also in Eq. 6, both terms $K_a/(K_a - \alpha)$ and $K_a/(K_a - \beta)$ become 1.

If both the absorption and distribution are very rapid, these terms can be ignored for simplicity, and a maximal steady state concentration can be easily predicted by omitting the $e^{-KT_{max}}$ term in the numerator of the above Eq. 3 even for the two compartment model. Because of this approximation, the predicted maximal concentration from this equation will be greater than that actually observed.

As discussed above, it is possible to design a dose with pharmacokinetic parameters alone. However, in some cases, pharmacodynamic considerations make the selection of the dose regimen deviate from this principle. If pharmacological half-life is substantially different from pharmacokinetic half-life, then pharmacodynamic half-life (instead of pharmacokinetic half-life) should be used. For example, aspirin is rapidly hydrolyzed to salicylic acid, but the half-life for antiplatelet activity is in days. Therefore, a small amount of aspirin once a day is a good dose regimen in order to achieve the desired pharmacological response. Another exceptional case is for the drugs that are relatively nontoxic even though the pharmacological activity is directly related to plasma concentrations (i.e., there is a large therapeutic index). In this case, a high dose can be given so that the dosing interval can be much longer than the elimination half-life. The half-life of penicillin G is less than 1 h, but it is given at very large doses every 6 or 12 h.

If absorption is slow, and the apparent absorption half-life is much longer than the elimination half-life, then the dose regimen can be based on the apparent half-life of the absorption phase. Changing the formulation is a relatively

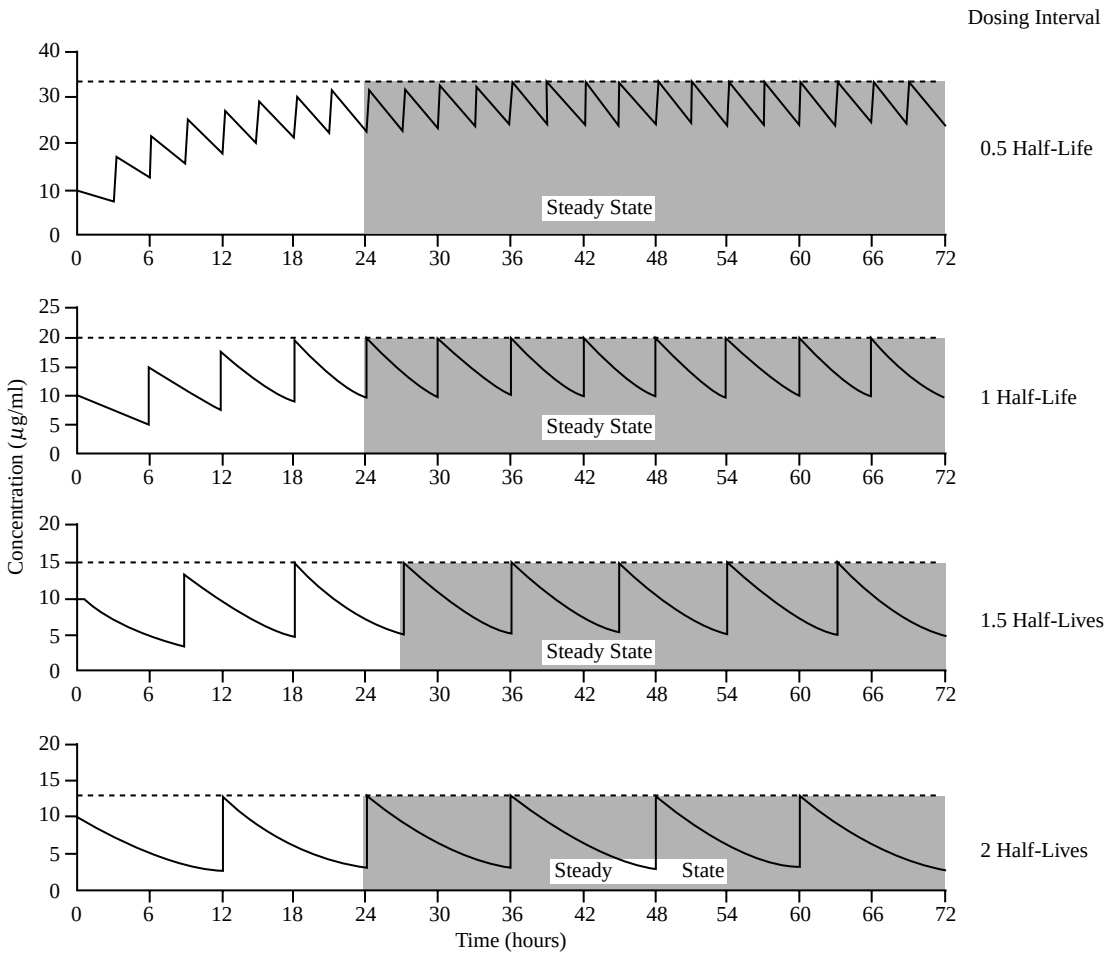

Fig. 1 Simulated plasma concentration-time curves obtained after repetitive doses were given at the intervals of every 1, 1.5, 2, and 3 half-lives. Steady-state levels were obtained between 4 (24 h) and 5 (30 h) half-lives, regardless of dosing interval. The accumulation factors (R) are 3.4, 2, 1.6, and 1.3 for dosing intervals of 0.5, 1, 1.5, and 2 half-lives, respectively.

common approach that is taken for short-acting drugs to extend the duration of absorption. The elimination half-life of nitroglycerin is approximately 2 min. However, nitroglycerin from a transdermal formulation is slowly released, and therapeutic plasma concentrations can be maintained for 24 h.

Another question regarding dose regimen is how often the dosage has to be changed and by how much. This can be usually determined using simple pharmacokinetic principles. The dose will not change by more than 50% and no more often than every 3 to 4 half-lives. Regardless of the half-life and frequency of dosing, it will take 3 half-lives to reach 87.5% of the steady state plasma concentration if the elimination rate constant is smaller than the absorption rate constant (Fig. 2). However, if the elimination rate constant is much greater than the absorption rate constant, the time to reach steady state will depend on the absorption rate constant and not on the elimination constant.

Loading Dose

The appropriate magnitude for the loading dose can be calculated as follows:

$$\text{Loading dose} = \text{Target plasma concentration} \times V_{ss}/F \quad (7)$$

To achieve steady-state plasma concentrations, it takes approximately 4 elimination half-lives. If the half-life is long and the drug effects are immediately required for treatment of a life-threatening condition, then single or multiple loading doses are sometimes inevitable. For example, the half-life of lidocaine is greater than 1 h.

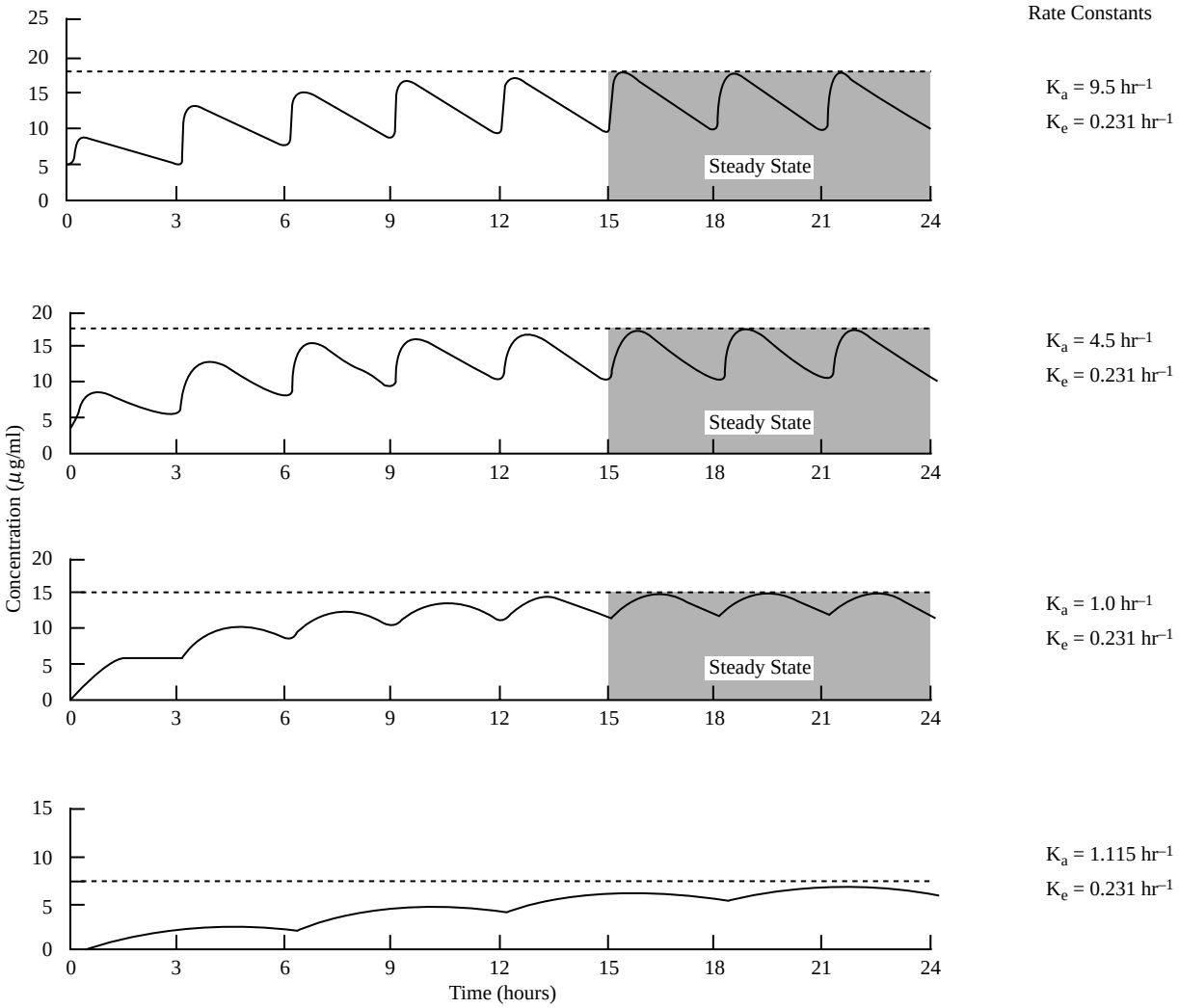

Fig. 2 Computer-simulated plasma concentration-time curves that show effects of absorption rate on the time to reach steady-state plasma concentrations. When absorption rate is higher than the elimination rate, the time to reach steady-state concentration is dependent on the elimination rate (top three figures). When absorption rate is lower than elimination rate, the time to reach steady-state concentration is dependent on the absorption rate (bottom figure).

However, a patient with arrhythmia after a myocardial infarction cannot wait 4–6 h to achieve therapeutic concentrations of the drug by IV infusion. Thus, the use of a loading dose of lidocaine in the coronary unit is a standard therapy.

For oral doses, the loading dose is usually twice that of the single dose. This is based on the pharmacokinetic principle that the accumulation factor is two when a drug is administered at every half-life. However, a loading dose should be cautiously used, particularly for those drugs with a narrow therapeutic window, because the sensitive individual may be exposed to toxic concentrations. Furthermore, for drugs with long half-lives, it will take a long time to eliminate a large loading dose from the body.

DOSE- (OR CONCENTRATION-)RESPONSE RELATIONSHIP

A drug is primarily carried by the blood from the absorption site to the target organ/tissue or blood component where the drug interacts with a receptor to produce its effect. Consequently, for many drugs, various types of relationships exist between the plasma or serum

concentration of a drug and its clinical efficacy and toxicity. Much effort has been directed toward establishing reliable mathematical relationships between drug bioavailability input (plasma concentrations) and pharmacological output (response) (1–3). Although the relationship is far from being completely understood, this dose-response relationship is very important in therapeutic decisions, and optimal dosage regimens can be deliberately planned for many drug therapies using the plasma concentration as a reasonable marker, particularly when pharmacological effects are easily measurable (e.g., blood pressure). This dose-response relationship generally depends on whether the plasma concentration is directly or indirectly related to response and whether a drug interacts with its receptor in a reversible or irreversible manner. If there is no apparent correlation between plasma/serum concentrations and the pharmacological effects and/or the effects are not easily measurable, the trial-and-error approach may be more practical.

Directly Reversible Pharmacological Response

The concept of a direct and rapidly reversible pharmacological response implies that the intensity of response is directly associated with the drug concentration at the site of action. In this category, two models (pharmacodynamic and pharmacokinetic–pharmacodynamic) are discussed.

In the pharmacodynamic model, the drug concentration at the receptor site is proportional to the drug concentration in the plasma, regardless of the pharmacokinetic model (one compartment or multicompartment), and the interaction between the drug and receptor is directly and rapidly reversible after drug administration.

Plasma concentration (C) and intensity (I) of the pharmacological response often follow an empirical relationship, known as the Hill equation:

$$I = \frac{I_{\max} C^n}{(C_{50}^n + C^n)} \tag{8}$$

where $I_{\max}$ is the maximal effect attributable to the drug and C_{50} is the concentration producing 50% of the maximum effect. Two examples of this are the in vivo effect of *d*-tubocurarine on muscle strength in patients and the plasma concentration–antiarrhythmic effect of tocainide in humans.

Another common and empirical relationship between concentration and response is the sigmoidal plot of response vs. logarithm of dose, plasma concentration, or drug concentration in the body. Very often, this curve shows excellent linearity from at least 20–80% of the maximum attainable intensity of response, which is a region of particular interest in drug therapy. Such apparent linearity between response and log plasma concentration has been demonstrated for a number of drugs, such as theophylline and propranolol. Relating response to the logarithm of plasma concentration rather than to the logarithm of dose reduces the variability in response due to differences in absorption, metabolism, and excretion among patients.

The pharmacokinetic–pharmacodynamic model is one in which drug concentrations at the effect site are not known or cannot be estimated without knowledge of the drug effect. If the pharmacological response is associated with a peripheral compartment (not with a central compartment) that receives a substantial mass of drug, a linear, log-linear, or sigmoidal relationship may also be obtained when the response is plotted against the calculated concentrations of the drug in the peripheral compartment (not plasma concentrations). A linear relationship was obtained between behavior response and the predicted concentration of the drug in the tissue compartment after IV administration of *d*-lysergic acid diethylamide (LSD) to humans.

Indirect Pharmacological Response

In contrast to the direct pharmacological responses discussed above, some pharmacological responses are indirect and represent the net result of several processes of which only one is influenced by the drug. In this case, a direct relationship between plasma concentration and pharmacological response may not be obtained. However, if the process influenced by the drug can be identified, then the drug concentration may relate to changes in this process. This concept is illustrated by the effects of oral anticoagulants such as warfarin.

Warfarin inhibits the synthesis of certain vitamin K-dependent clotting factors. However, warfarin has no effect on the physiological degradation of these factors. Therefore, the pharmacological response of warfarin should be based on the inhibitory effect on the synthesis of the clotting factor (prothrombin) rather than on the change in clotting time. These mechanism-based models were found to be relevant for the clinical effects of numerous drugs (4). Many metabolic and endocrine systems provide similar modeling strategies (5).

Irreversible Pharmacological Response

Most drugs produce a reversible pharmacological response. However, some antibiotics, irreversible enzyme inhibitors, and anticancer agents incorporate irreversibly or

covalently into a cell's metabolic pathway. This results in an irreversible effect—cell death. Complex kinetic models are used to explain the relationship of dose-chemotherapeutic effects for some drugs, such as methotrexate, cyclophosphamide, and arabinosylcytosine (2).

FACTORS AFFECTING DRUG RESPONSE

Dosage regimens are generally derived using average pharmacokinetic parameters to maintain plasma concentrations of the drug within the therapeutic window. For many drugs, both therapeutic range and toxic concentrations have been established (6). However, for a fixed dose, the plasma concentration of a drug within a patient can be influenced by many pharmacodynamic and pharmacokinetic factors. Therefore, these factors must also be taken into consideration for maintaining desired therapeutic concentrations of a drug.

Pharmacokinetic Factors

Factors affecting absorption

Factors affecting drug absorption include formulation, disease state, food effect, and drug–drug interaction. Formulations used for oral administration include solutions, suspensions, capsules, and uncoated and coated tablets. Depending on the formulation of a drug, the absorption characteristics may differ substantially. Slow-release oral formulations are often used to prolong the drug's activity and to reduce the fluctuation between C_{max} and C_{min} values.

Intestinal surgery and disease states have been shown to alter the absorption of some drugs, although information on this subject is limited. For a given disease state or surgery, drug absorption may be increased, unchanged, or decreased, depending on the drug. Therefore, the effect of a particular disease condition on drug absorption cannot usually be predicted from the existing information.

The effect of food on the absorption of a drug from the gastrointestinal (GI) tract is quite variable and depends on the physicochemical properties of the drug substance and the mechanism by which it is absorbed. The presence of solid food in the stomach will tend to decrease the rate of stomach emptying and thus delay the absorption of the drug, which often results in decreased systemic availability of the drug. The relative bioavailability of lincomycin is reduced to about 60% when given 1 h before breakfast and to about 20% when given immediately after breakfast, compared with that observed after oral administration to fasting subjects. A potentially dangerous situation may arise owing to delayed absorption of hypnotic agents in nonfasting patients. With the hypnotic capuride, a 42-min difference in onset of absorption has been observed between fasting and nonfasting subjects.

The presence of food is also found to increase gastrointestinal motility and splanchnic blood flow up to 30%. Consequently, the absorption of some drugs is either unaffected or increased by food. Among the beta-blocking agents, absorption of bevantolol and oxprenolol was unchanged with food, whereas absorption of metoprolol, labetalol, and propranolol was increased, but the absorption of atenolol and sotalol was decreased. The oral absorption in humans of the antifungal antibiotic griseofulvin is substantially greater with food of high fat content than without food. Because a high fat concentration in the small intestine stimulates bile secretion, absorption of the relatively lipophilic drug may be increased by enhancing its dissolution in the GI tract. Furthermore, the increase in splanchnic blood flow resulting from food consumption may contribute to the enhanced absorption. However, relatively polar and poorly permeable drugs show a tendency toward reduced absorption in the presence of food (7). Food decreases absorption of alendronate, astemizole, captopril, didanosine, and penicillamine.

Food effects on drug absorption will depend not only on the physical and chemical properties of the drug substance but also on the formulation. Following oral administration of theophylline, the absorption rate of the drug can be either increased or decreased with food, depending on the formulation (8). Generally, the greatest food effect is observed when the drug is taken immediately after a meal; the degree of interaction decreases as the time between eating and drug-dosing increases (9). Extensive reviews of the effect of food on drug absorption can be found in the literature (10–12).

Drug interaction is another important factor affecting absorption. In general, interactions that interfere with absorption either involve binding or chelation of drugs in the GI tract, rendering them nonabsorbable, or involve effects on gastric emptying or gastrointestinal motility. In addition, gastric pH changes may affect on the absorption of some drugs.

Antacids, particularly aluminum hydroxide gel, reduce the absorption of most tetracycline drugs by forming an insoluble complex in the gut. Simultaneous administration of iron (ferrous sulfate) with tetracycline, oxytetracycline, methacycline, or doxycycline seriously impairs the absorption of these antibiotics. Adsorbants such as kaolin (an antidiarrheal agent) substantially reduce the absorption of lincomycin and promazine. Ion-exchange resins, such as

cholestyramine, strongly bind many anionic and neutral drugs in the GI tract and interfere with the absorption of anticoagulants and thyroxine. Imipramine significantly reduces bioavailability of levodopa in humans, presumably because delayed absorption by reducing gastric emptying time enhances metabolism of levodopa in the gut. Orally administered ketoconazole requires an acidic medium to dissolve adequately and, therefore, antacids, anticholinergic drugs, H2 blockers, or acid pump inhibitors (e.g., omeprazole) will reduce the bioavailability of this drug. Metoclopramide, cisapride, and cathartics increase GI motility and may decrease the absorption of drugs that require prolonged contact with the absorbing surface and those that are absorbed only at a particular site along the GI tract. Anticholinergics decrease GI motility and may increase absorption by prolonging contact with the area of optimal absorption or may reduce absorption by slowing dissolution and gastric emptying. The interactions between drugs have been reviewed in detail (13–15).

Factors affecting distribution

After entering the general circulation, a drug is carried throughout the body and is distributed to various tissues. The drug distribution depends on the relative affinity of binding to plasma protein, red blood cells, and tissues. However, it can be altered in the presence of other drugs, in some disease states, and due to the age of the patient.

The risk of interactions resulting from the displacement of the drug from proteins is significant, primarily with drugs that are highly protein-bound (>90%) and that have a small apparent volume of distribution and a relatively narrow therapeutic window. This can result in a high concentration of unbound drug temporally (the first few days), which may have clinically important effects. Trichloroacetic acid, a major metabolite of chloral hydrate, displaces warfarin from its binding sites on plasma albumin. This displacement temporarily elevates plasma levels of warfarin and, thereby, increases the pharmacological effect per unit dose. Administration of 1 g of choral hydrate daily for 1 week to subjects on warfarin increases the hypothrombinemic effect by 40–80%. When valproic acid and phenytoin are coadministered, unbound phenytoin concentrations increase significantly in some patients causing more adverse reactions, even when total phenytoin serum concentrations are within the usual therapeutic range.

Disease states are another factor that may affect the binding of drugs to proteins in plasma and other tissues. Unusually low binding of drugs to plasma proteins has been observed in various diseases. For example, the percentage of unbound phenytoin in plasma was 5.8–7.3% in normal subjects, whereas the percentages of unbound drug in patients with renal diseases (azotemia or uremia) were 8–25%. In addition to renal diseases, liver diseases, hyperbilirubinemia, and hyperlipidemia are reported to lower plasma protein binding of some drugs. However, during physiological stress (e.g., myocardial infarction, surgery, ulcerative colitis, and Crohn's disease), the plasma protein binding of basic drugs (e.g., propranolol, quinidine, and disopyramide) increases, and volume of distribution decreases accordingly due to the increase in concentrations of the α1-acid glycoprotein.

Age-elated changes in drug distribution have been reported. The apparent volume of distribution is somewhat larger in newborns and infants than in adults. The estimated volume of distribution of sulfamethoxypyridazine in newborns and infants is 0.47 and 0.36 L/kg, respectively, whereas the values are 0.20–0.26 L/kg in children, adults, and elderly subjects. The volume of distribution of chlordiazepoxide is substantially larger in the elderly (0.52 L/kg) than in the young (0.42 L/kg). The age-related difference in the volume of distribution may be due to a difference in plasma protein binding and/or in the relative size of body compartments.

Factors affecting metabolism

Drug metabolism is a primary mechanism for removal of drugs from the body. Drug metabolism may be affected by age, disease state, polymorphism, and inhibition or induction of drug-metabolizing enzymes. Sex differences in drug metabolism are minor in humans and usually are not clinically important.

Although hepatic drug metabolism is generally slower in neonates as compared with adults, children actually metabolize certain drugs more rapidly than adults. The half-life of theophylline averaged 3.7 h in children but ranged from 5 to 9 h in nonsmoking adults. Children also metabolize antipyrine, clindamycin, diazoxide, and phenobarbital more rapidly than adults. In elderly subjects, metabolism of some drugs (e.g., amobarbital, antipyrine, phenylbutazone, and chlordiazepoxide) has been reported to be less efficient than in younger subjects. Thus, the aging process may reduce the total clearance of a drug and extend its elimination half-life. After oral administration of amobarbital, the mean percentages of the dose excreted as the hydroxy metabolite in 0–24 h urine specimens was reduced from 14% in the younger subjects (20–40 years of age) to only 4% in the elderly subjects (>65 years of age). The apparent elimination half-life of chlordiazepoxide showed a strong correlation with age, increasing from a mean of 9.5 h in the young to 37 h in the elderly. Consequently, the plasma concentrations of these drugs were greater in the elderly subjects than in the younger subjects.

Genetic polymorphism in metabolism is a very important factor in the variability in drug elimination. The metabolism of isoniazid (and other drugs that have a hydrazine moiety such as sulfamethazine, sulfapyridine, hydralazine, procainamide, and dapsone) is more rapid in some individuals than in others. The major route of elimination of isoniazid in humans is via metabolism to acetylisoniazid by hepatic *N*-Acetyltransferase; thus, the half-life of the drug depends on how rapidly the drug can be acetylated. In about 50% of the U.S. population and in 5–10% of the Asian population, hepatic *N*-acetylation is slow. In those with extensive (rapid) metabolism, the half-life of the drug is 45–80 min, whereas in those poor (slow) metabolism, the half-life is 140–200 min. Slow acetylators require a longer time to acetylate these drugs and, therefore, are more susceptible to adverse effects caused by the parent compound (e.g., peripheral neuritis with isoniazid, lupus erythematosus with hydralazine or procainamide, and sedation and nausea with phenelzine). Compared with slow acetylators, the rapid acetylators require larger and more frequent doses of such a drug in order to obtain the desired therapeutic response.

Drugs that are metabolized by the cytochrome P-450 (CYP) isoenzymes CYP2D6, CYP2C9, and CYP2C19 also exhibit genetic polymorphisms. An example of CYP2D6 metabolism is debrisoquine. In about 5–10% of Caucasians in North America and Europe and about 1% of Asians, 4-hydroxylation of debrisoquine is reduced, and such individuals are at increased risk for toxicity (orthostatic hypotension). Beta blockers (metoprolol and timolol), antiarrhythmic drugs (encainide and flecainide), tricyclic antidepressants (amitriptyline, nortriptyline, and desipramine) and an antitussive drug (dextromethorphan) are also metabolized by CYP2D6. Therefore, in the CYP2D6 poor metabolizers, unusually large therapeutic responses and/or more adverse effects may be observed compared to extensive metabolizers.

Phenytoin is metabolized by CYP2C9. In CYP2C9 poor metabolizers, increased toxicity (e.g., excessive CNS depression) was observed. *S*-mephenytoin is stereoselectively metabolized by CYP2C19. About 3–5% of Caucasians in North America and 20% of Asians metabolize mephenytoin slowly, which increases their risk of a major side effect (transient sedation). In such persons, other drugs metabolized by the same isoenzyme as mephenytoin will also be poorly metabolized, and pharmacological activity and/or side effects of these drugs may be increased. These drugs include mephobarbital (an anticonvulsant), proguanil (antimalarial), and possibly diazepam (an anxiolytic). These drugs have a substantially longer half-life in poor metabolizers than in extensive metabolizers. Thus, caution must be used for the patient with limited capacity of metabolism.

Other genetic polymorphisms include deficiencies in aldehyde dehydrogenase-2 (an enzyme involved in ethanol metabolism), alcohol dehydrogenase (another enzyme involved in ethanol metabolism), glucose-6-phosphate dehydrogenase (G6PD), or glutathione synthatase. Patients with G6PD deficiency (about 10% of Black males) are at increased risk of developing hemolytic anemia when given oxidant drugs, such as antimalarials (e.g., chloroquine, pamaquine, and primaquine), aspirin, probenecid, and vitamin K. Patients with low levels of glutathione synthetase in hepatocytes are at increased risk of liver damage if given drugs metabolized by glutathione conjugation, such as acetaminophen and nitrofurantoin.

Some disease states may have clinically significant effects on drug metabolism. If hepatic metabolism is an important route of drug elimination, any dysfunction of the liver may lead to a change in the pharmacokinetics of that drug, and subsequently plasma concentrations of the drug will be different from those in a patient with normal liver function. The clinical significance of the changes in drug elimination depends on the type or severity of the disease. Antipyrine has often been used as a model drug for the investigation of the effects of liver disease on oxidative drug metabolism in humans. In healthy subjects, the average half-life of antipyrine is approximately 12 h. In contrast, the half-life of the drug in patients with liver cirrhosis or chronic active hepatitis averages 34 and 26 h, respectively. However, the half-life of antipyrine does not provide a quantitative index of the degree of impairment of drug elimination in a patient for a specific drug. Some other examples of drugs whose half-lives in patients change due to impairment of metabolism in particular disease states include hexobarbital in hepatitis, meperidine in liver cirrhosis, propranolol in chronic liver diseases, and rifampin in obstructive jaundice.

Enzyme induction or inhibition is another factor that alters the rate of metabolism of many drugs. Many drugs, polycyclic hydrocarbons, insecticides, and other environmental chemicals (e.g., cigarette smoke) stimulate activity of microsomal enzymes in the liver. Consequently, repetitive administration of certain drugs or continuous systemic exposures to certain chemicals may facilitate elimination of other drugs by increasing their metabolism. Phenobarbital and other barbiturates are among the most potent and widely studied inducing agents in humans. During repetitive administration of phenobarbital (2 mg/kg/day) for a period of 4 weeks, a substantial decrease in the efficacy of warfarin was observed after the first week, as shown by a substantial decrease in mean prothrombin time. Rifampin also induces metabolism of

warfarin. After administration of 600 mg of rifampin a day to subjects receiving repetitive daily doses of warfarin, plasma concentrations of warfarin were reduced to near nondetectable levels.

Some drugs, such as rifampin, induce their own metabolism. During repetitive administration of rifampin at a daily dose of 600 mg for 30 days, the elimination half-lives of rifamprin were 4.2 and 1.9 h on the first and last days, respectively. Carbamazepine also shows pronounced self-induction. The plasma concentrations at steady state predicted from single-dose data were two to three times higher than the actual concentrations observed during chronic treatment.

Whereas the clinical consequence of enzyme induction is usually a decrease in the efficacy of the drug, inhibition of drug metabolism can lead to serious adverse effects from the accumulation of drugs to toxic concentrations. However, by identifying the CYP isozymes responsible for metabolism of substrates and inhibitors and determining their in vitro inhibition constants, it is possible to predict clinically significant drug interaction in many cases. Chloramphenicol is a potent inhibitor of the metabolism of CYP2C9 substrates (e.g., tolbutamide, phenytoin, and dicumarol) in humans. Treatment with 2 g of chloramphenicol for several days resulted in a marked rise in the steady state serum concentrations of tolbutamide and phenytoin. The area under the plasma concentration-time curves of tolbutamide was elevated five-fold by coadministration of sulfaphenazole.

Among the CYP isozymes, CYP3A4 is responsible for the metabolism of the widest range of drugs and endogenous compounds in humans. It accounts for 60% of CYP isoforms in human liver. Therefore, if a drug is metabolized by CYP3A4, concomitant administration of other drug that is metabolized also by CYP3A4 may result in a drug interaction. For example, ketoconazole inhibited metabolism of the nonsedating antihistamines terfenadine and astemizole, and cisapride. As a result of CYP3A4 inhibition, life-threatening arrhythmic side effects of these drugs occurred. An extensive review of clinically significant drug interactions can be found in the literature (16).

Factors affecting excretion

Renal excretion of drugs is accomplished by both a pH-dependent diffusion and active secretion. Changes in urine pH may occur due to disease states, dietary factors, or simultaneous administration of drugs. The effect of urinary pH change on the elimination rate of acidic and basic drugs can be pronounced and may be predicted according to the pH partition hypothesis as long as excretion of the drug in urine is an important route of elimination.

For an acidic drug, a more alkaline urine increases ionized drug concentration and decreases reabsorption at the distal tubule. Consequently, elimination of the drug will be faster. On the other hand, more acidic urine leads to a decreased concentration of the ionized acidic drug, resulting in increased reabsorption and slower elimination. After sulfaethidole was administered to humans, the half-life decreased from 11.4 to 4.2 h when urinary pH increased from 5 to 8, respectively. The elimination rates of sulfalene and sulfasymazine were doubled by the administration of sodium carbonate, which increased urine pH from 6 to 8. Elimination of salicylate was slower in humans with low urine pH, and higher plasma concentrations were achieved.

For basic drugs, urinary excretion increases with low urinary pH and decreases with high pH. As a result, patients receiving amphetamines or closely related drugs may be placed at risk by relatively small changes in urine pH. Patients with alkaline urine had intense psychoses lasting more than 3 days after the last dose of amphetamine.

Age-related alteration of renal function is a very important factor in selecting the dose regimen. Renal function in newborns is incompletely developed. Neonatal renal plasma flow and glomerular filtration rates (normalized for body surface) are only 30–40% of those of adults. The half-life of penicillin G is 3.2 h in newborns (up to 6 days of age) and 1.4 h in infants (14 days of age or older), whereas in older children and adults, it is about 0.5 h. The mean half-life of gentamicin is about 5 h in newborns under 1 week of age and about 3 h in infants 1–4 weeks of age. The half-life of gentamicin in older infants and adults is approximately 2 h. Thus, drugs that depend on renal excretion as the principal mode of elimination would be expected to have a longer residence time in infants.

Impaired renal function may affect drug elimination to varying degrees, depending on the extent of the contribution of renal clearance to the total clearance. The greater the contribution of the renal clearance to the total clearance, the greater the influence of renal disease will be on drug elimination and steady state concentration in the plasma during repetitive dose administration.

Pharmacodynamic Factors

There are many examples of drugs that interact at a common receptor site or that have additive or inhibitory effects. Also, there are some other interactions of an apparently pharmacodynamic nature whose mechanism is poorly understood.

Monoamine oxidase (MAO) inhibitors, such as, phenelzine or tranylcypromine, cause norepinephrine to accumulate within adrenergic neurons. Thus, drugs that release norepinephrine (e.g., indirectly acting sympathomimetic amines, amphetamine, and phenylpropanolamine) can produce an exaggerated response including severe headache, hypertension, and cardiac arrhythmias. MAO inhibitors are present in many over-the-counter drugs for cold, allergy, and diet products, and patients taking MAO inhibitors should avoid such products.

OPTIMIZATION OF DOSAGE REGIMENS FOR INDIVIDUAL PATIENT

Dose regimen is determined using the average pharmacokinetic parameters. However, unpredictable variation exists even among normal individuals. For many drugs, one standard deviation in the values observed for F, CL, and V_{ss} is about 20%, 50%, and 30%, respectively. Therefore, 95% of the time, the C_{ss} that is achieved based on average pharmacokinetic parameters will be between 35 and 270% of the target concentration. This is not an acceptable range, especially for the drugs with narrow therapeutic index. If F, CL, and V_{ss} can be directly measured and the dose is further adjusted for body weight or surface area, drug–drug interactions, and disease state, such as renal impairment (for renally excreted drugs), then a more precise dose regimen can be made for a particular patient.

Dosage Adjusted for Body Weight

The same amount of drug in different individuals can result in different drug concentrations in plasma, because the apparent volume of distribution of a drug depends on the size of the body compartment as well as on the relative binding of the drug in the vascular and extravascular spaces. The volume of total body water and extracellular fluid in subjects with a normal lean to fat ratio is directly proportional to body weight. A relationship exists between the apparent volume of distribution and body weight, as well as between steady state plasma concentration and body weight. To maintain the therapeutic plasma concentration at the steady state in nonobese adults, it is better to determine the dose on a mg/kg body weight basis than to administer a fixed dosage per patient.

The distribution of relatively polar drugs (e.g., digoxin and gentamicin) is limited to body water, whereas highly lipid–soluble drugs (e.g., thiopental) distribute into fat. Therefore, for polar drugs, the use of lean body mass instead of total body weight allows for a more predictable dose–response relationship in obese patients. In fact, if digoxin dosage for obese individuals is calculated on the basis of total body weight, plasma concentrations of the drug may be dangerously high.

The percentages of fat and lean body mass in an individual may be estimated with the help of (Eqs. 9 and 10).

$$\%\ \text{Fat} = 90 - 2(H - G) \tag{9}$$

where H is height and G is girth, both in centimeters, using umbilical level at expiration.

$$\text{Lean bodymass} = (100 - \%\ \text{fat}) \times \text{weight(in kg)} \tag{10}$$

Dosage adjusted for body surface area

Children require and tolerate a larger mg/kg dose than adults and cannot be considered as small adults. For example, the doses of digoxin required to maintain mean plasma concentrations of about 1–1.5 ng/ml are 15–20 μg/kg per day for children 4 weeks to 2 years of age, 10–15 μg/kg per day for children 2–12 years of age, and 4–5 μg/kg per day for adults. Reasonable estimates of the doses required in children are often obtained by calculating the child's dose on the basis of body surface relative to that of an adult. An estimate of body surface area may be made from Eq. 11.

$$S = (W^{0.425} \times H^{0.725} \times 71.84)/10^4 \tag{11}$$

where S is surface area in m^2, W is body weight in kg, and H is height in cm. The approximation of the body surface area for children can be obtained using the simplified (Eq. 12).

$$S = 0.088\, W^{0.728} \tag{12}$$

The body surface area of the average adult is usually taken to be 1.73 m^2.

In general, for the average 3-month-old child weighing 6 kg, the body surface-adjusted dose is 2 times greater than the mg/kg dose given to an average adult, whereas for the average 5-year-old weighing 20 kg, the body surface-adjusted dose is 1.5 times greater than the mg/kg dose. The requirement of larger mg/kg doses in children than in adults may be related in part to the fact that total body water and extracellular fluid make up a higher percentage of the total body weight in children than in adults.

Dosage adjusted for drug interactions

Epidemiological studies demonstrate that if 5 or fewer drugs are coadministered, the rate of drug-related adverse

reactions is approximately 4%. However, when 20 or more drugs are prescribed, the rate of adverse reactions increases to 45%. Therefore, patients should take as few drugs as possible for concurrent use. If more than one drug therapy is required and interactions between the coadministered drugs are known to be clinically significant, the dosage of one or more drugs may be increased or decreased based on the clinical response and severity of side effects in the individual patient, or each drug may be administered with a certain time interval, depending on the situation during the concurrent therapy. After one or more drugs is discontinued, the dosage regimen of the other drug(s) may be readjusted for continuing therapy. If a drug or a particular formulation of a drug is known to have a food effect, the drug or formulation must be given at least 1 h prior to or after food intake for reliable therapy.

Dosage adjusted for renal impairment

The renal clearance of the drug is proportional to endogenous creatinine clearance, irrespective of the mechanisms (i.e., filtration, reabsorption, or secretion), and the creatinine clearance is used as an indicator of the severity of the disease. Furthermore, it is possible to predict the half-life of a drug in a patient with renal disease based on the creatinine clearance and on a knowledge of the pharmacokinetics of the drug in normal subjects, as illustrated with cefazolin in Fig. 3.

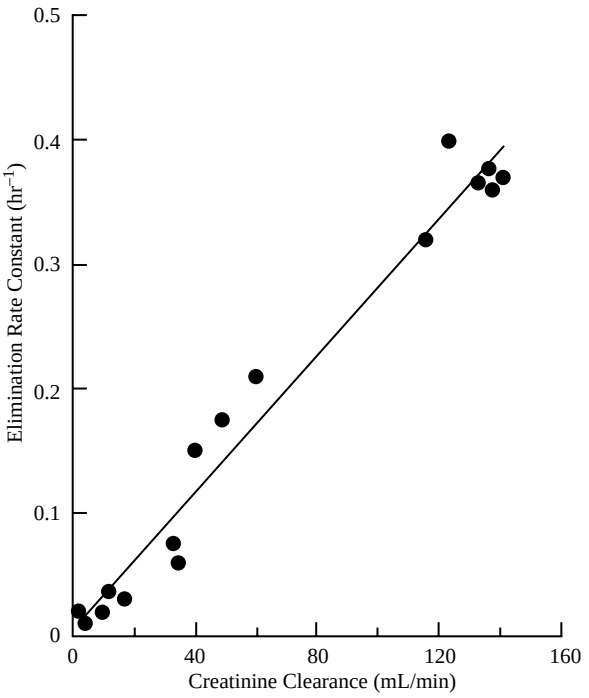

Fig. 3 Relationship between renal function (expressed by creatinine clearance) and overall elimination rate constant for cefazolin after a single intramuscular injection. (From Ref. 17.)

The half-life of some drugs is changed sufficiently in patients with impaired renal function to warrant consideration of a change in the usual dosage regimen, thus preventing toxic accumulation of the drug in the body. Changes in regimen usually take the form of reducing the dose per dosing interval or increasing the length of the dosing interval. Either change is usually roughly proportional to the relative difference in half-life between the patients with and without renal disease. Cephalexin is administered as a 250-mg to 1-g dose every 4–6 h. Its average half-life in patients with normal renal function is about 0.5–1 h. In a patient with a creatinine clearance of 10–15 ml/min, the half-life of the drug increased about eightfold because cephalexin is eliminated almost entirely by urinary excretion of the parent drug. The dosing frequency suggested for this patient is the usual dose every 24 h, which is 3–6 times longer than the usual dosing interval. A comprehensive guide to drug usage in adult patients with impaired renal function is available (17).

Dosage adjustment for other diseases

If the major route of elimination of a drug is by metabolism in the liver and the patient has liver dysfunction, then dosage of the drug or frequency of dosing may be reduced. However, unlike patients with renal dysfunction, the degree of impairment of drug elimination in an individual with liver dysfunction cannot be predicted. In general, little change is necessary in dosage regimens when liver disease is inactive, although doses should be kept low, and particular care should be taken with sedative and antidepressant drugs. When liver disease is present, the dosage regimens of some drugs (e.g., sedatives and analgesics) in each patient should be titrated to his or her clinical response. In selected instances, plasma concentrations of the drug should be monitored and dosage regimens adjusted based on plasma concentration measurements.

It is generally recommended that altered plasma protein binding in the disease state does not require dosage adjustment. However, in patients with hypoalbuminemia, the incidence of drug toxicity appears to be increased, and, thus, dosages should be reduced. Patients showing toxicity may have impaired elimination in addition to altered plasma protein binding. In fact, it has been suggested that low serum albumin concentrations may be a marker for the integrity of liver function.

REFERENCES

1. Holford, N.H.G.; Sheiner, L.B. Clin. Pharmacokinetics **1981**, *6* , 429–453.
2. Gibaldi, M.; Perrier, D. *Pharmacokinetics*; Marcel Dekker, Inc: New York, 1982.
3. Sheiner, L.B.; Stanski, D.R.; Vozeh, S.; Miller, R.D.; Ham, J. Clin. Pharmacol. Ther. **1979**, *25* , 358.
4. Jusko, W.J.; Ko, K.C. Clin. Parmacol. Ther. **1994**, *56*, 356–358.
5. Carson, E.R.; Cobelli, C.; Finkelsten, L. *The Mathematical Modeling of Metabolic and Endocrine Systems*; John Wiley & Sons: New York, 1983.
6. Benet, L.Z.; Sheiner, L.B. Design and Optimization of Dosage Regimens: Pharmacokinetic Data. *The Pharmacological Basis of Therapeutics*, 7th Ed.; Gillman, A.G., Ed.; Macmillan Publishing Co.: New York, 1985; 1663–1733.
7. Lee, K.H.; Xu, G.X.; Schoenhard, G.L.; Cook, C.S. Pharm. Res. **1997**, *14*, 1030–1038.
8. Cook, C.S.; Hauswald, C.L.; Grahn, A.Y.; Kowalski, K.; Karim, A.; Koch, R.; Schoenhard, G.L.; Oppermann, J.A. Inter. J. Pharm. **1990**, *60*, 125–132.
9. Karim, A.; Burns, T.; Janky, D.; Hurwitz, A. Clin. Pharmacol. Ther. **1985**, *38*, 642–647.
10. Welling, P.G. J. Pharmacokinet. Biopharm. **1997**, *5*, 291–334.
11. Toothaker, R.D.; Welling, P.G. Ann Rev. Pharmacol. **1980**, *20* , 173–199.
12. Fleusher, D.; Zhou, Y.; Pao, L.H.; Karim, A. Clin. Pharmacokinet. **1999**, *36* , 233–254.
13. Griffin, J.P.; D'Arcy, P.F.; Speirs, C.J. *A Manual of Adverse Drug Interactions*, 4th Ed.; Butterworth & Co.: Oxford, UK, 1988.
14. Grahame-Smith, D.G. *Drug Interactions*; The Macmillan Publishing Co: New York, 1977.
15. Prescott, L.F. Drugs **1973**, *5* , 161–186.
16. Michalets, E.L. Pharmacotherapy **1998**, *18* , 84–112.
17. Bennett, W.M.; Singer, I.; Coggins, C.H. JAMA **1973**, *223* , 991–996.
18. DeVane, C.L.; Jusko, W.J. Dosage Regimen Design. *Pharmacokinetics: Theory and Methodology*; Rowland, M., Tucker, G., Eds.; Pergamon Press: Oxford, UK, 1986; 213–233.
19. Holford, N.H.G.; Sheiner, B.L. Kinetics of Pharmacologic Response. *Pharmacokinetics: Theory and Methodology*; Rowland, M., Tucker, G., Eds.; Pergamon Press: London, UK, 1986; 189–212.
20. Welling, P.G. *Pharmacokinetics*; American Chemical Society: Washington, DC, 1986; 7–76.
21. Rowland, M., Tozer, T.N., Eds. *Clinical Pharmacokinetics Concepts and Applications*; Williams and Wilkins: Media, PA, 1995.